Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Encephalopathy of Prematurity

Miami Neonatology 2018 – 42nd Annual International Conference

Overview

Brain injury is an important driver in adverse neurodevelopmental outcomes in infants, and specifically in preterm infants. The goal of current research is to identify how to reduce adverse experiences that negatively influence brain development.

Terrie Inder, MBChB, MD, discusses the importance of reducing both traditional and invisible brain injury in premature infants. Dr. Inder specifically reviews encephalopathy of prematurity and the drivers to improve outcomes.

Content Areas

- Assessing early degeneration in preterm brains
- Discerning forms of brain injury
- Recognizing potential invisible injuries
- Understanding what drives improved outcomes in the NICU experience
- Applying methods to reduce pain and stress from NICU procedures
- Addressing the NICU experience, parenting, and family environment

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Describe the forms of neonatal brain injury and the nature of alterations in brain development
- Recognize potential causes of invisible brain injury in preterm infants
- Discuss adverse and positive NICU experiences on preterm infants.

Faculty

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The following have no significant relationship to disclose:
Erin Allen, MS, RD, LDN (RD reviewer)
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This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on March 15, 2019 and is eligible for credit through March 15, 2021.

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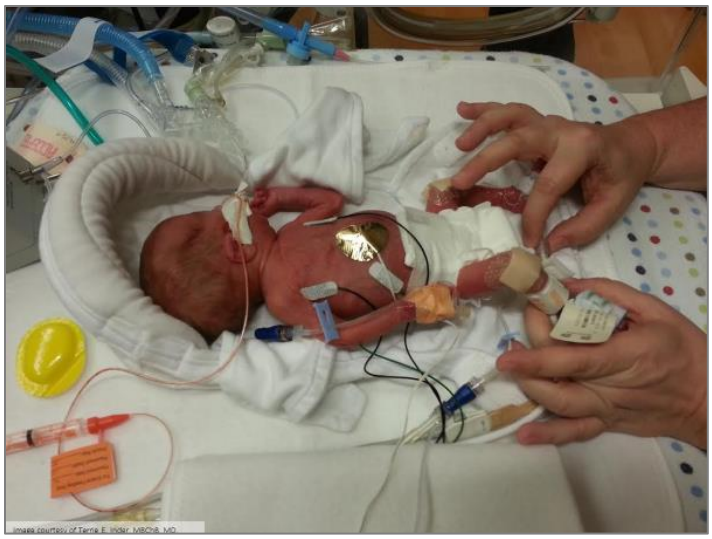
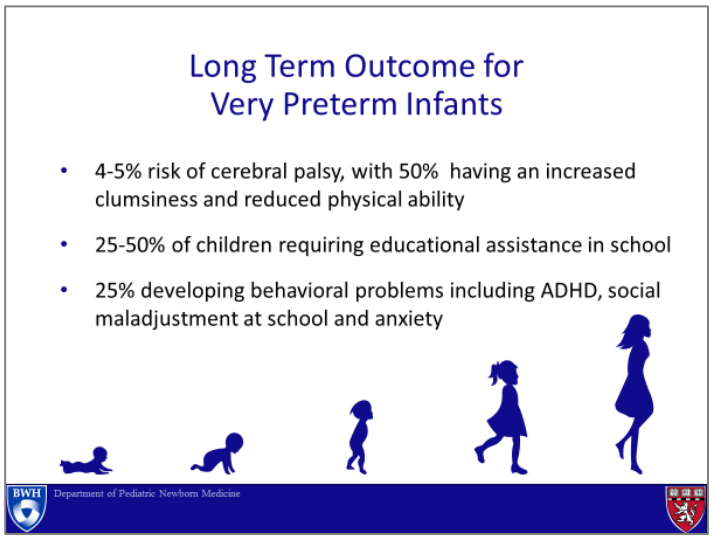
Editor's Note: This is a transcript of the live presentation from Miami Neonatology on November 12, 2018.

Dr. Terrie Inder: This is a big topic. In fact, it's my whole career I feel like I'm going to try and cover! But, we know why we're here. We care for many of these very small people, and we know that they face challenges as they go home.



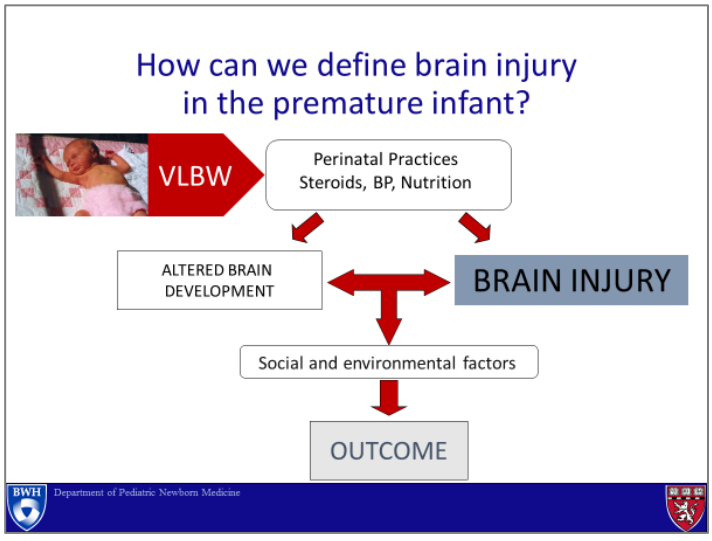
Slide 1

It's interesting, as we think whether it's the gut or the lung; now, I think the most important organ—the brain. Many of these things are set by the time the children are discharged from us, as you'll see in this talk. Our children face a lot of difficulties with physical clumsiness, educational needs, and, increasingly, we recognize the behavioral and mental health issues.



Slide 2

This is where we started. This little baby, actually, is my youngest daughter [Slide 3]. This is where I feel like I started the journey working with Joe Volpe to try and understand how to prevent these disabilities.[1] This was focused around brain injury. If we could get rid of brain injury, all our children would grow up and do very well.



Slide 3

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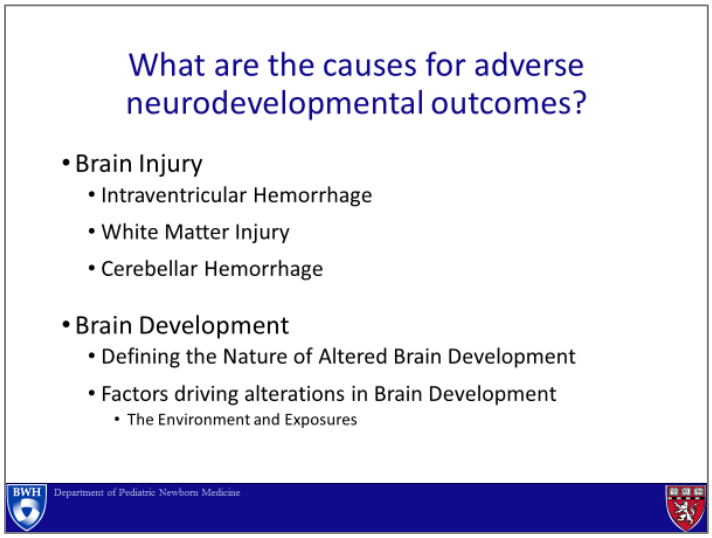
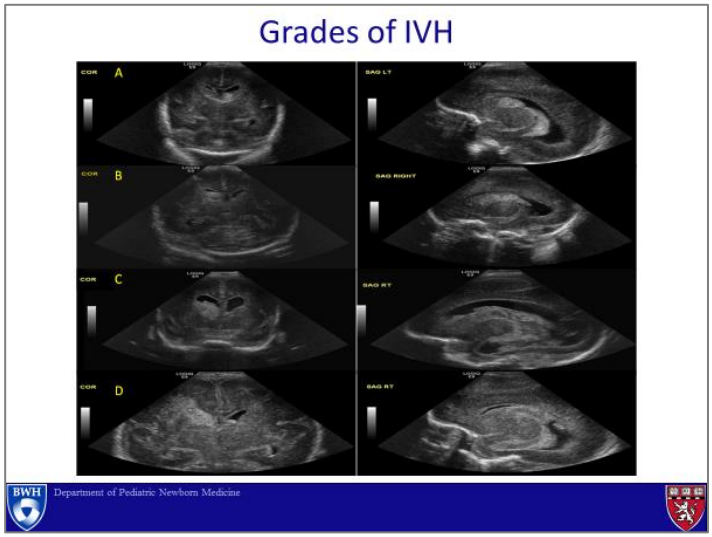
What do I mean by brain injury? At the time, that was predominantly intraventricular hemorrhage [IVH], and increasingly we recognized white matter injury. Now, we recognize cerebellar hemorrhage, as well. But I'm going to focus on those and other forms of brain injury that we don't recognize as well, before moving on to focus where I think our field has taken us, which is brain development.



Slide 4

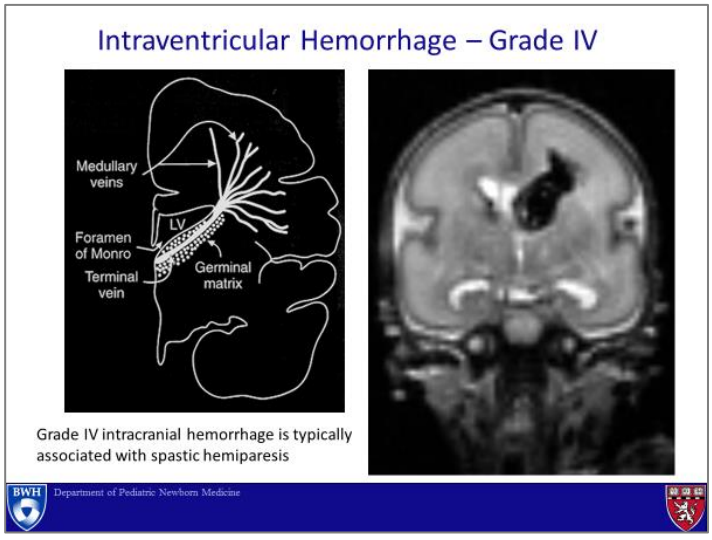
Intraventricular Hemorrhage (IVH)

Let's start with IVH. You're all familiar with this. The common ultrasound grading based on the Papile CT definitions with grade I, II, III, and so-called IV, which is really a parenchymal stroke.



Slide 5

You can see here the grade IV [Slide 6] is not an extension of the hemorrhage into the brain tissue, but rather an obstruction of the terminal vein, and a secondary stroke, venous stroke, in the parenchyma.



Slide 6

We know this condition is common, and over the last 20 years in our smallest infants we haven't really made a huge impact in reducing the incidence of this disorder, which is still occurring in about 25% of our very preterm infants less than 28 weeks. This is despite many changes in practice, including

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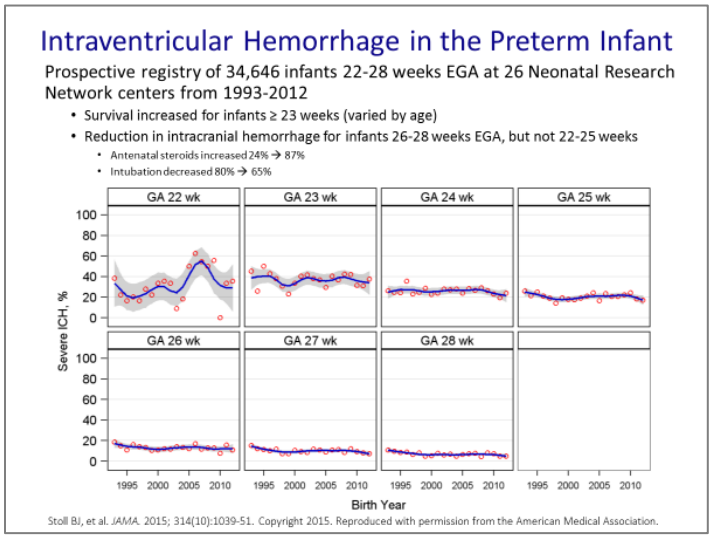
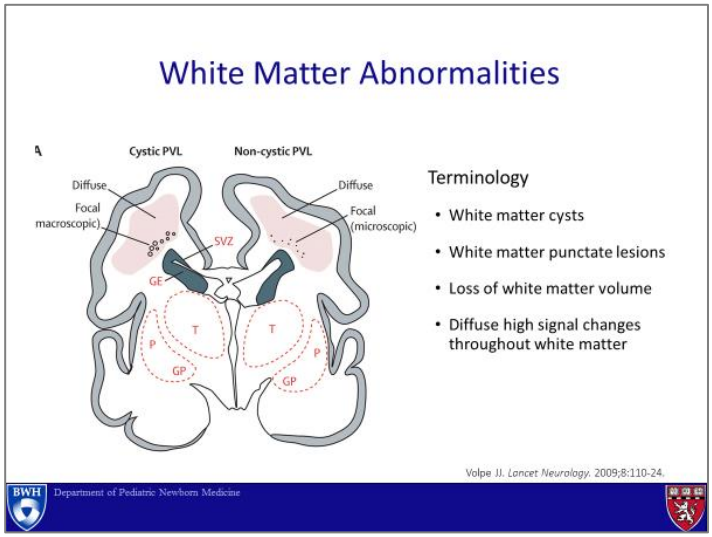
widespread use of antenatal steroids, which have been associated with 50% reduction in the risk of IVH, and changes in our respiratory management.[2] We still have a way to go, and I'll come back and touch on that at the end of this talk.



Slide 7

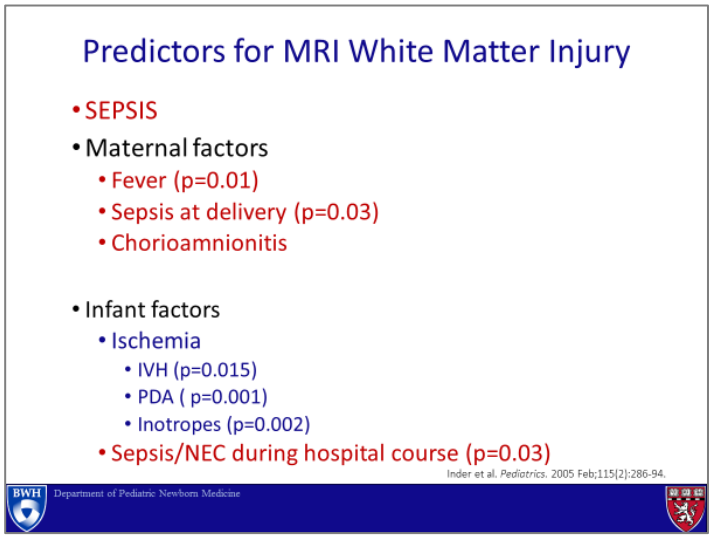
Periventricular Leukomalacia (PVL)

Periventricular leukomalacia, so-called because it's around the ventricle. White: bad! [It] became increasingly recognized because of MRI, which gave us a window to identify this type of brain injury and moved us away from just the form of recognizing cystic white matter lesions to that of the more subtle punctate spots and dots, and the loss of white matter volume.



Slide 8

The predictors for white matter injury focus around some of the things we've already heard today, particularly around infection and inflammation, although ischemia is still important. But the most common form of severe white matter injury now, I see in association with necrotizing enterocolitis [NEC]. I would say, just as you have heard the beautiful talk about treating NEC for the bowel, NEC's biggest effect actually occurs in the white matter. Any infant who has been exposed or treated for medical NEC should immediately alert you to looking more carefully with MRI at the brain.



Slide 9

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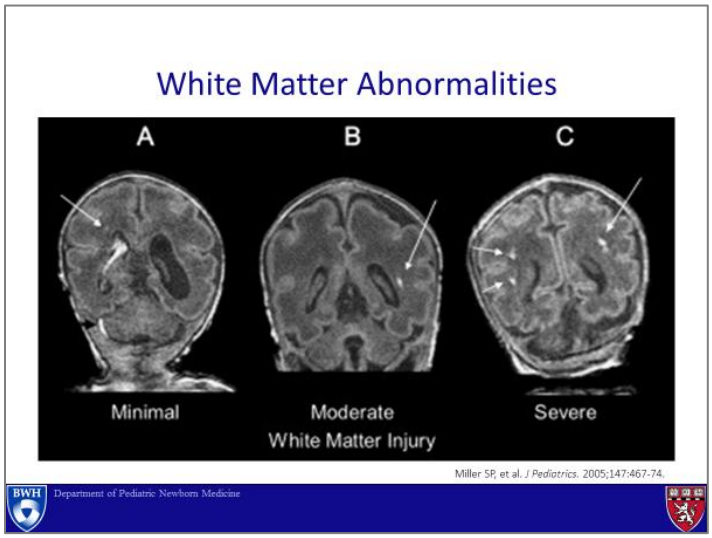
These are some of the things you may see in terms of punctate lesions. You can see here [Slide 10]—either a single spot or a large spot or multiple spots—these are believed to be scars, small scars, in the developing cabling network of the brain.

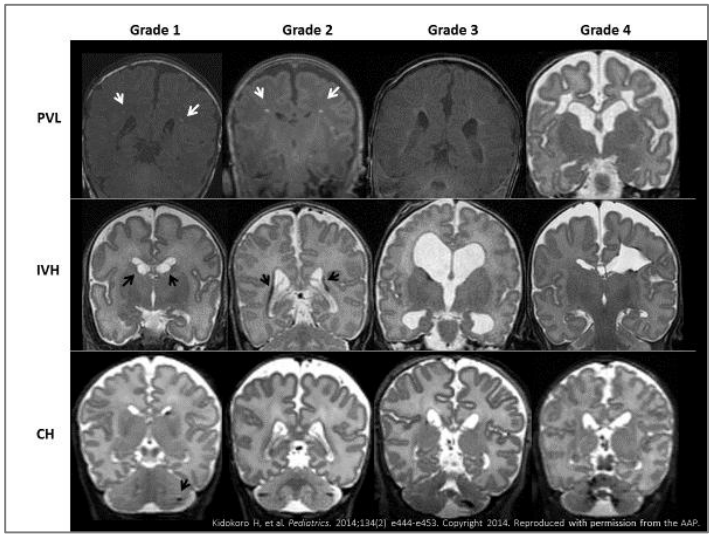


Slide 10

Is brain injury the major factor driving adverse neurodevelopmental outcome?

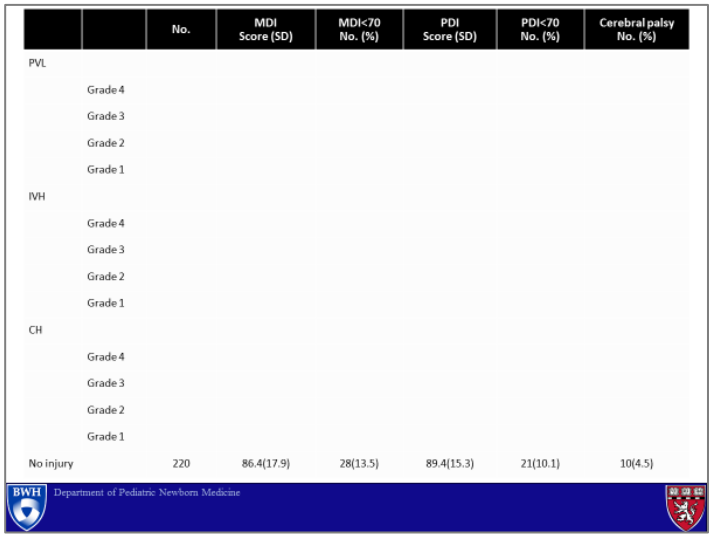
I said brain injury was important in driving the adverse neurodevelopmental outcomes that we see. How do we see that? Let's look at these common forms of brain injury—white matter injury, IVH, and cerebellar hemorrhage—and see whether they are the thing that's really driving our adverse outcomes.

You can see here [Slide 11], on the top is white matter injury, graded from the more benign, little spots, all the way through to the severe cystic form; IVH with the classical grading; and cerebellar hemorrhage, which we increasingly recognize now with MRI, as either focal lesions, in one hemisphere being small or through to very large, bilateral hemispheres.



Slide 11

We did this in 340 premature babies at term equivalent, looking at an MRI at term.[1] The first thing we found was that 220 of those premature babies didn't have any form of injury at all, which is wonderful, right?



Slide 12

But look at their outcomes 2 years after discharge from the neonatal intensive care unit. As you can see there [Slide 12], their MDI [Mental Developmental Index] or their IQ was 86. Now, you all know, it should be at least 100, right? That's 14 points below normal. Indeed, nearly 15% of these

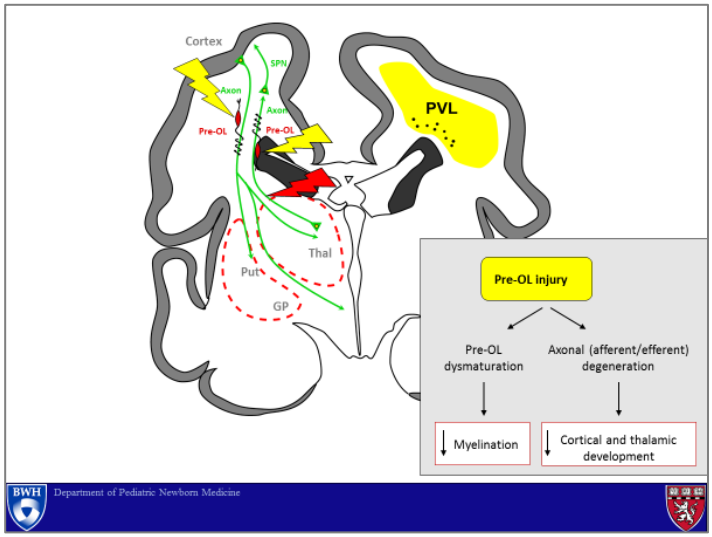
children would have been labeled as intellectually disabled. If you go right across, 5% of them were labeled with cerebral palsy. So, if brain injury is the answer to all of the difficulties our children face, why were so many of them below what they should have been and suffering difficulties?

When we put in all the children with injury, you could see that there was a downward deviation for worse outcomes with high-grade injury, both for IVH and white matter lesions. The lower grades, at least with these crude forms of testing, did not show deviation. This means, out of those 340 babies, the small number who had high-grade injuries, certainly, were more dramatically affected. But for the rest of the children, it wasn't injury that was driving their adverse outcome.

		No.	MDI Score (SD)	MDI<70 No. (%)	PDI Score (SD)	PDI<70 No. (%)	Cerebral palsy No. (%)
PVL		34					
	Grade 4	4	49.3(18.5)	3(75.0)	49.3(18.5)	3(75.0)	4(100)
	Grade 3	5	61.2(20.4)	3(60.0)	55.6(29.4)	4(80.0)	4(80.0)
	Grade 2	14[c]	82.6(13.5)	3(21.4)	85.1(11.5)	1(7.1)	3(21.4)
	Grade 1	11[d]	85.7(20.5)	2(18.2)	86.2(18.3)	1(9.1)	1(9.1)
IVH		53					
	Grade 4	13	76.1(22.6)	4(30.8)	72.3(16.2)	4(30.8)	6(46.2)
	Grade 3	2	72.5(5.0)	2(100)	75.5(12.0)	1(50.0)	1(50.0)
	Grade 2	16	85.6(15.4)	1(6.3)	89.7(11.8)	0	1(6.3)
	Grade 1	20	88.1(14.1)	3(15.0)	90.9(12.4)	2(10.0)	1(5.0)
CH		22					
	Grade 4	1[e]	84	0	84	0	0
	Grade 3	2[f]	75.5(10.6)	1(50)	77.0(1.4)	0	1(50.0)
	Grade 2	4[e]	88.8(6.7)	0	95.3(12.2)	0	1(25.0)
	Grade 1	15[b]	84.3(15.6)	4(26.7)	87.4(17.6)	3(20.0)	2(13.3)
No injury		220	86.4(17.9)	28(13.5)	89.4(15.3)	21(10.1)	10(4.5)

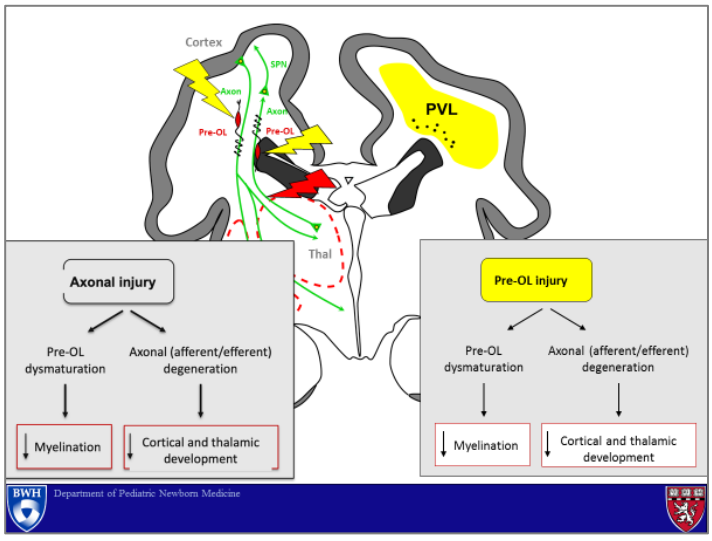
Slide 13

We have to remember that we only have some visibility for certain forms of injury. When you look here in the brain [Slide 14], you can see the cortex, the computer drivers, the gray matter on the outside of the brain.[3] The white matter, where we have this injury, which is composed of cables and little cells that wrap around to produce myelin. We can't see a lot of the types of injury; we can't see directly those cells that are going to produce the myelin; and we can't see if they've been injured.



Slide 14

We know if they are injured, not only will it impair their capacity to produce myelin, but it may impair the signaling going up and down to those critical gray neurons in the thalamus and in the cortex. In addition, the axon might be injured, the actual cable. Again, that will have effects, and we can't see that either.



Slide 15

More dramatically, we know that there are areas we don't even look at, at the moment, like the thalamus, that are injured. Again, there will be

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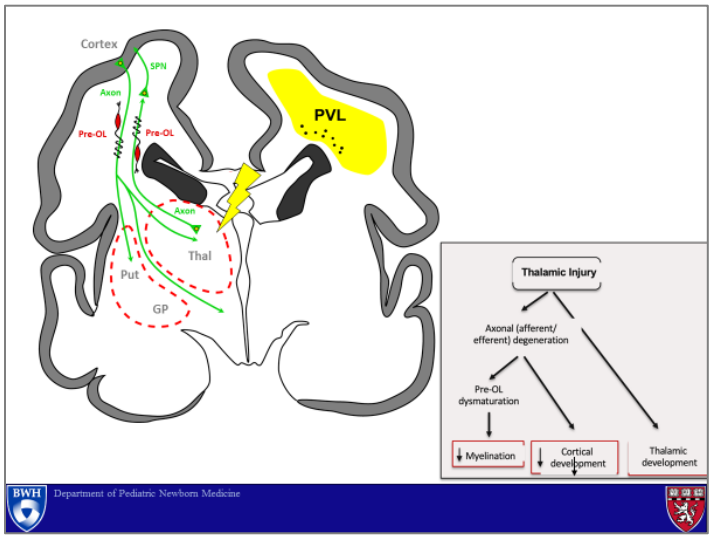
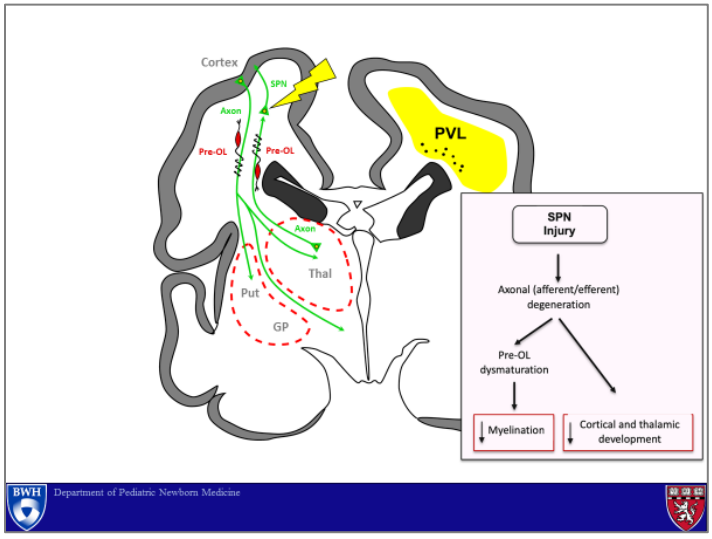
effects up and down, both into the cortex and down into other areas of the brain.



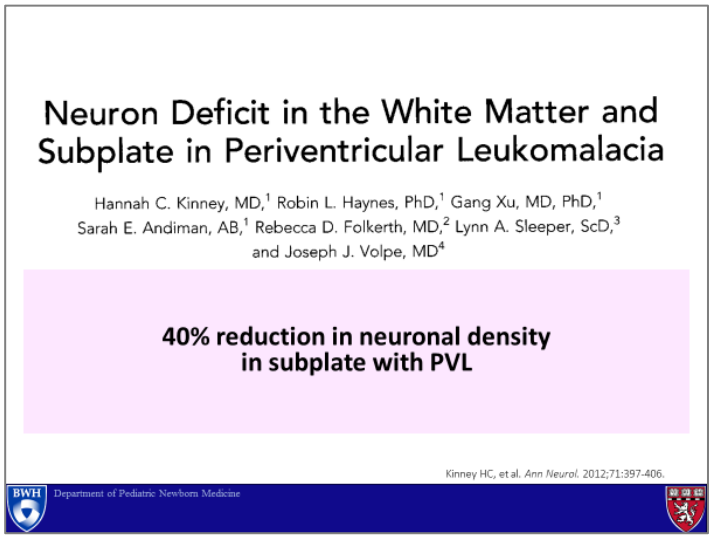
Slide 16

In addition, if we look carefully under the microscope at the brain, there are deep layers in the cortex that are guiding the cortex's connections and developments in the so-called subplate that are present all the way up to 30 weeks. If they are interfered with, again, we're going to affect the way the rest of the brain is wired and developed, particularly the cortex, and the way we think.



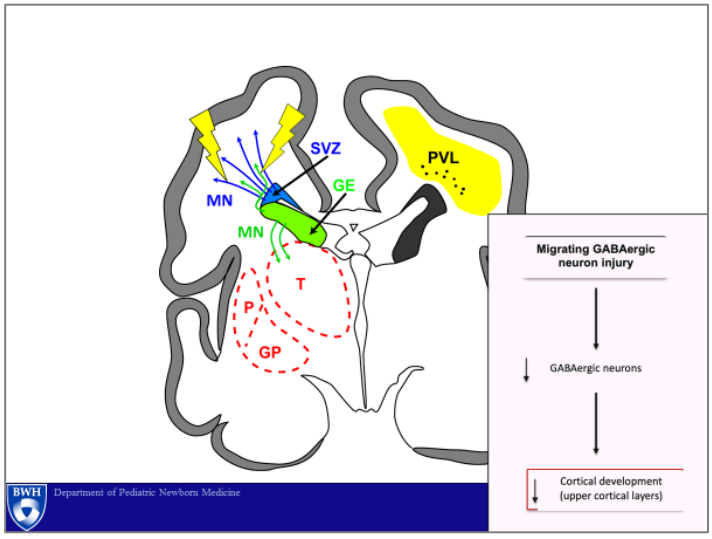
Slide 17

Indeed, that's been shown that if you look at this region in infants who have passed away, there's a 40% reduction in those cells in that region.[4]



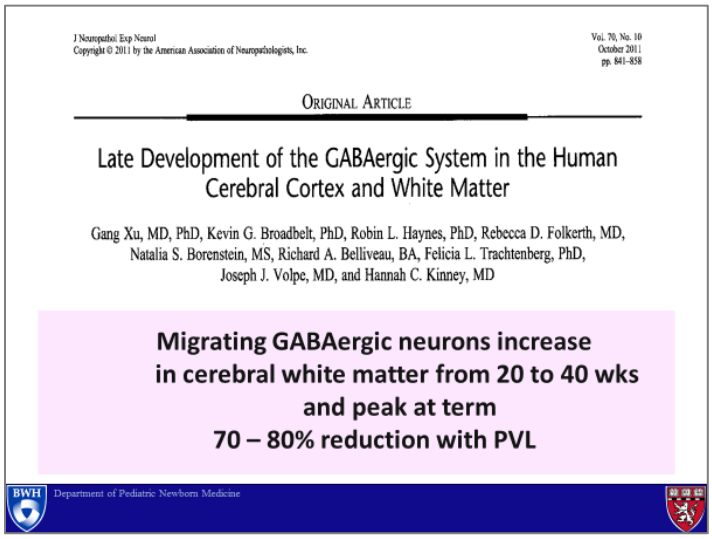
Slide 18

Finally, the germinal areas of the brain that we used to believe finished their work by 18 weeks, have now been shown to be producing critical interneurons, critical neurons that are traveling out right up to the time of term. Indeed, if they are injured, then we're going to affect the signaling within the cortex.



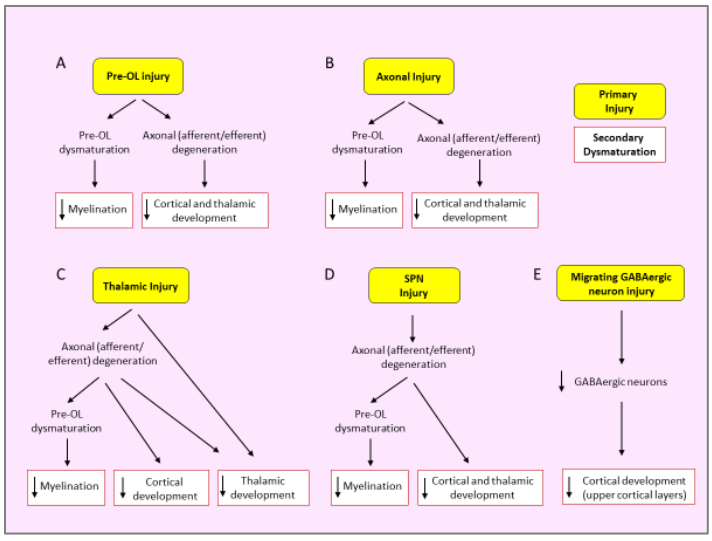
Slide 19

Again, it's been shown when you look at our babies that pass away, there's a 70%–80% reduction in those cell types in that area.[5]



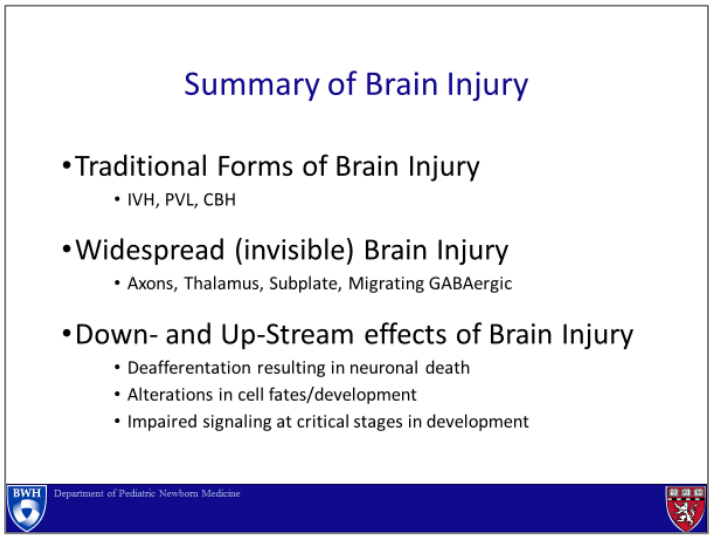
Slide 20

All of these areas are vulnerable to injury.



Slide 21

Indeed, when we think about brain injury, often, we only talk about IVH. But, there's a lot more widespread, invisible, brain injury going on in our babies during these early days and weeks of life, that are currently invisible by our imaging techniques, that have dramatic effects on development, both downstream and upstream, as the rest of the brain is developing, affecting the way we wire and signal at critical stages.



Slide 22

Can we define the nature of alterations in brain development—the role of advanced imaging?

I really want to move on... there is definitely an element of this injury that's invisible to us; but, can we start to understand what might be visible to us and what might be driving any alterations and brain development? To do that, we've had the privilege of being able to image babies in the neonatal intensive care unit repeatedly throughout their development. This is one infant imaged 3 times [Slide 23], and you can see the dramatic change in brain development.

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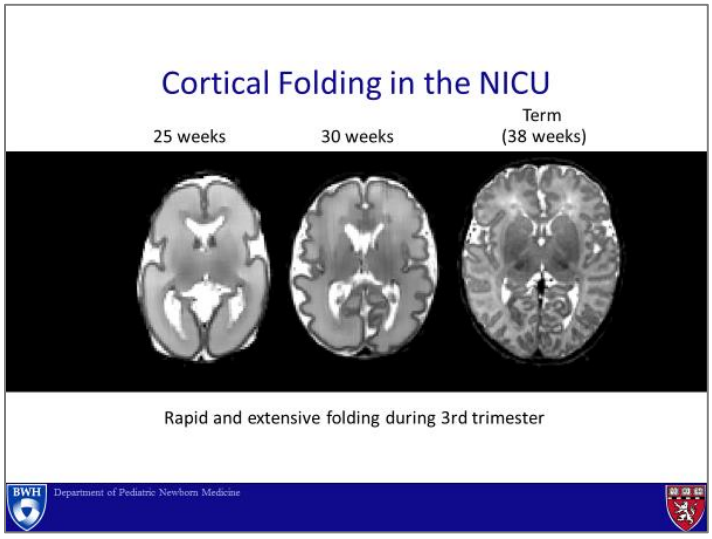
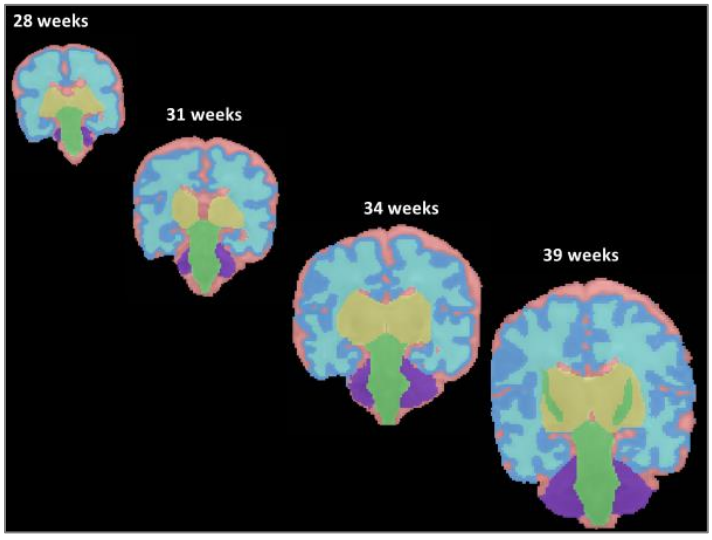


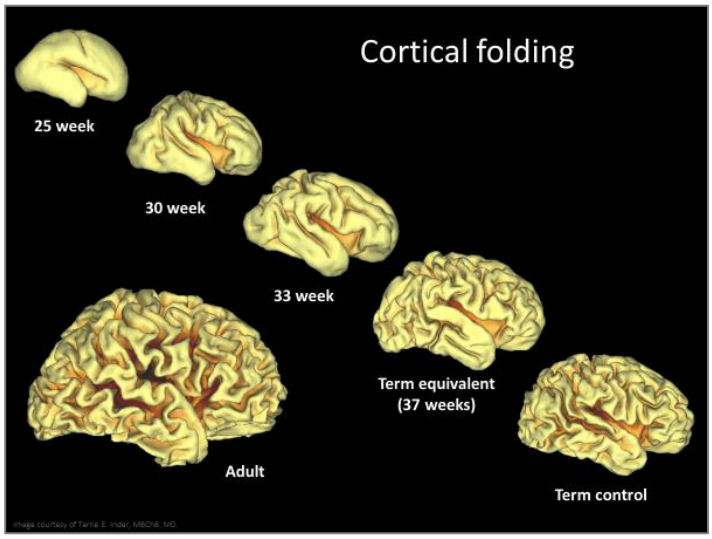
Slide 23

In fact, here's another baby imaged 4 times [Slide 24], and we can take the brain tissue types. You can see here now in the darker blue, the cortex, the gray matter, the light blue, the cabling, the gray matter in the thalamus, and basal ganglia in yellow, and the cerebellum in purple.



Slide 24

We can also look by mapping the surface of the brain. We can see the dramatic change in the brain from the 25-week infant through to term equivalent, how complex the folding is. Just as it has already been pointed out today, we can look at a healthy term baby and see how all the foundations for the adult brain are already in place by term equivalent.



Slide 25

We can take these types of images and say, so what are the differences if you're born prematurely compared to being born at term? Let's take a nice healthy term brain, and let's look at its surface. Let's take the first 5 premature babies who went home from St. Louis Children's Hospital and map them and see where the differences lie. I think when you see these 5 brains, none of these 5 brains had IVH or PVL [periventricular leukomalacia]. They all had pretty okay kind of neonatal courses. But, when you look at these brains, you can see that there's regions in the brain that haven't developed in the way they should have, right? In particular, you can see around the temporal lobe, these areas here, that are too smooth or very underdeveloped.

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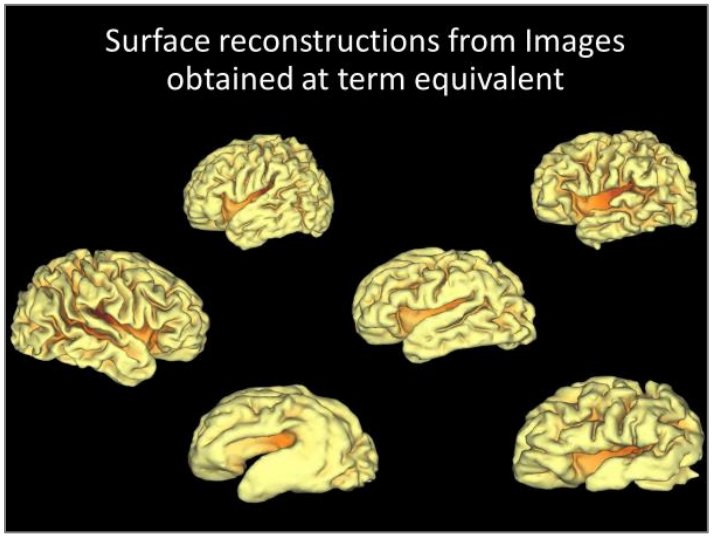
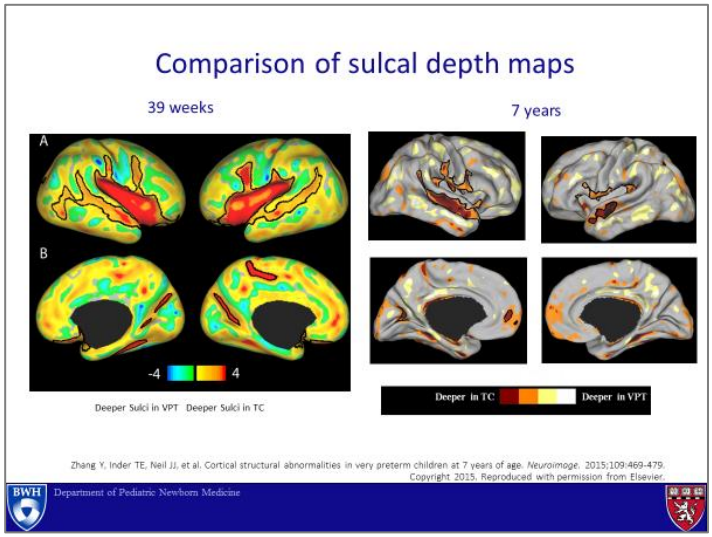


Slide 26



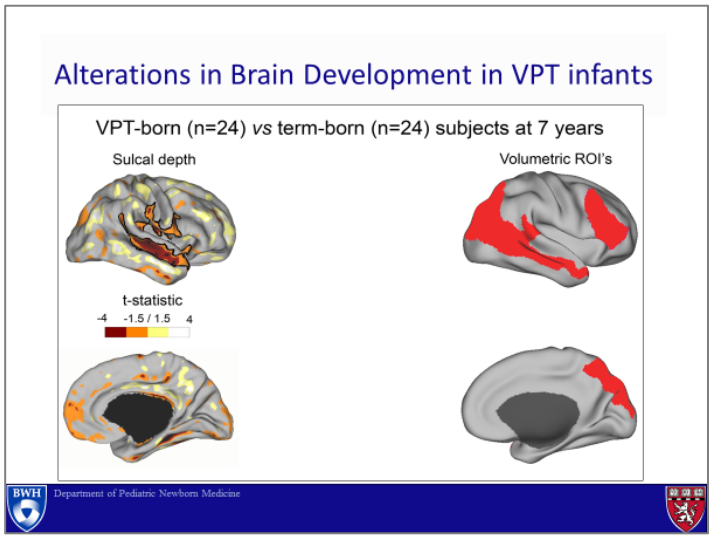
Slide 27

To try and define this more carefully, we took 54 prematurely born babies with no brain injury at term equivalent, and we compared them to 24 healthy term born babies, and we said, where is the brain different?

At term equivalent, as a prematurely born baby without injury, how is your brain different to a healthy term baby? The area that was dramatically different is shown here [Slide 27], along the superior temporal sulcus. Now, this area in the human brain is really important and distinguishes us as humans because it's involved in language; it's involved in facial recognition and social communication. It's very higher order in terms of evolution. We said, okay, well our poor babies have had a pretty rough time; we'll just give them a little bit more time to catch up.

We gave them 7 years to see whether they would catch up. By imaging and comparing prematurely born children to term born children 7 years after discharge from the neonatal intensive care unit, and what you can see is that same region is different 7 years after discharge from the neonatal intensive care unit.[6]

So, it is altered by the time you leave the neonatal intensive care unit. It persists all the way through childhood. It doesn't matter whether we compare it by looking at the surface or looking at the regions by volume reduction. This temporal area and a little bit into the dorsal prefrontal are altered by preterm birth, and they persist. They correlate with language and cognition.



Slide 28

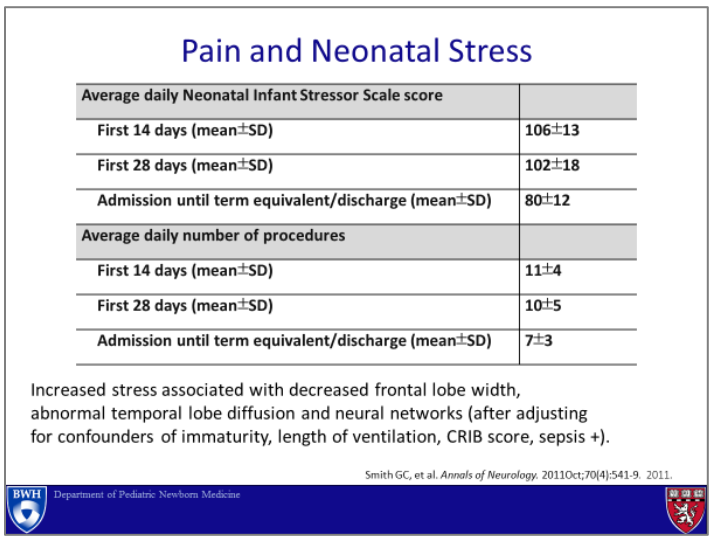
Encephalopathy of Prematurity

Are traditional medical factors mediating the alterations in brain development?

We found some deviations in brain development. That's fine. Let's just find out what it is that's causing that; stop doing it; and then everybody will be better, right? It's really kind of been a I-can-go-home, no-more-job. All good.

We had a medical student who came to work with us, and she decided she would start looking at something she thought was important for our babies, and that was how stressed they were. I was like, "What do you mean? I'm the one that's stressed. They're all right." She was like, "No. Look how much happens to them." So, we developed a stressor scale in concert with our nurses that weighted all the experiences every baby had every day, and we measured the scale with our nursing staff every 12 hours.

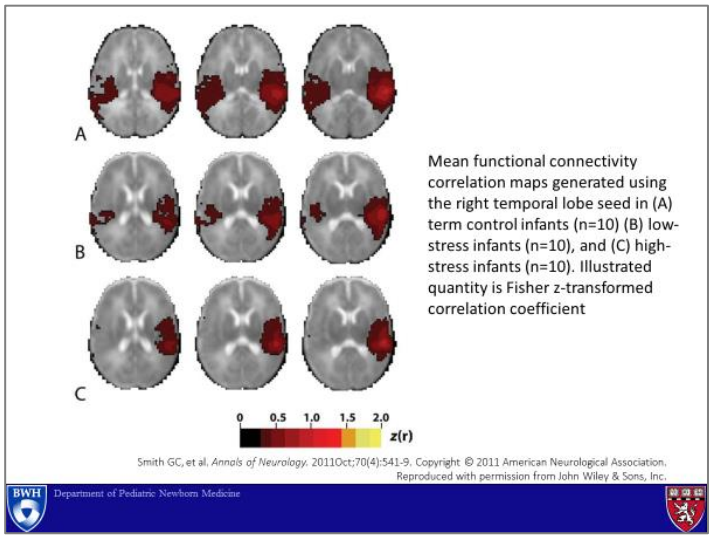
Now, the scale itself at the top there won't mean much to you except you can see that the first 28 days of life are pretty bad, and they're pretty similar, whether it's the first 14 or the first 28 days. What most people can relate to is the number of painful procedures, which you can see is between 10 or 11 a day.[7]



Slide 29

What we showed was that the amount of stressful exposure was associated with deviations in frontal and temporal lobe brain development. Initially, we just said, "Well, of course, if you're having more things done to you, it's because you're sicker and it's just a measure of how sick you are." We tried to control for all of that: How small you were, how long you were on the ventilator, how sick you were, everything. Nothing took away from this finding.

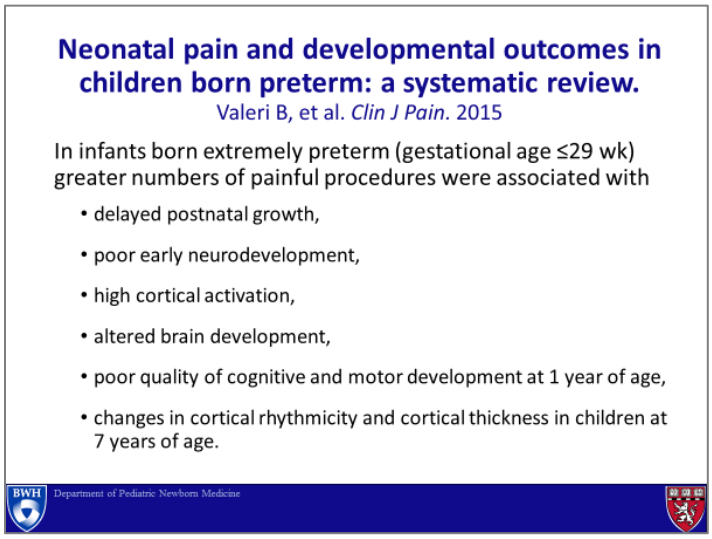
Here's an example of what it looks like [Slide 30]. This is a measure of brain connectivity. In *A* is a healthy term brain. What we do is we put a little box in the brain, and we ask the brain, where else in the brain the blood flow—just resting, just lying in the scanner—the resting blood flow is the same frequency. Guess what? All of our brains are so sophisticated in the way they're built that when I do that in your temporal lobe, your other temporal lobe says, "Oh, I'm in tune with you. I like you. We're not directly physically connected, but we got this. We do the same thing. We're in tune."



Slide 30

The preterm baby who had low-stress exposure in *B*, is not as strong; they're trying, but they're a little bit weaker. In *C*, the high-stress baby, nobody's in tune.[7] Totally lost the capacity to be in tune.

Now, there is a lot of other data out there about neonatal pain and its adverse effects on brain development measured in many different ways.[8]

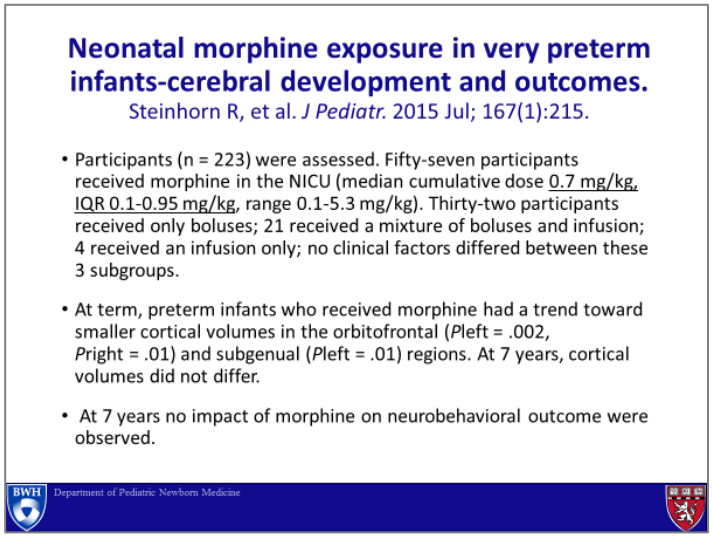


Slide 31

If the infants are suffering from pain, then should we provide analgesia?

I'm sure you're thinking if the babies are just in pain, why don't we give them appropriate analgesia, and then maybe that'd make everybody feel better, and they'd build better temporal lobes?

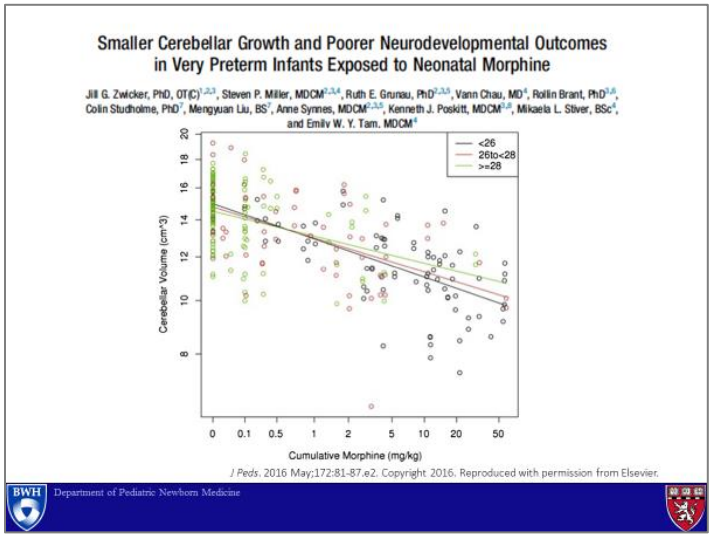
We had the pleasure of having my moderator's daughter spend time with us, which was absolutely fantastic because her child is as smart as her mother. She took data from 223 premature babies we had who received morphine during their neonatal course. You can see [Slide 32] the doses on median were 0.7 mg/kg, but ranged between 0.1 mg/kg and nearly 1 mg/kg, and that most of this was just intermittent and not often an infusion. We looked at the imaging findings and what we found was, early on, the babies had smaller cortical volumes, but by 7 years, Dr. Steinhorn now found no difference.[9] At 7 years, we found no impact on their outcomes. Now, that's good; it wasn't adverse, but it also wasn't beneficial, at least in these infants who received it.



Slide 32

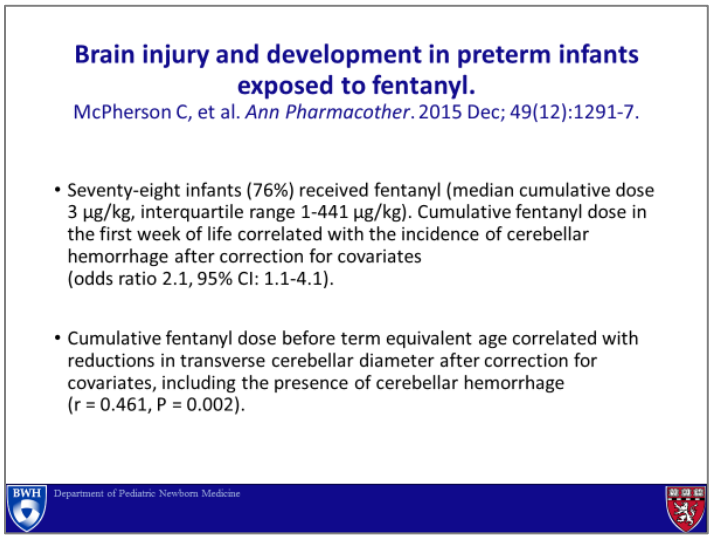
About the same time that our data was published, the Canadians came out with their data.[10] What they showed was an adverse effect. That adverse effect was most striking on the cerebellum. They showed that as the dose of morphine increased, there was impairment in the cerebellar growth. You can see, in contrast to our data—our data, remember, was 0.7 mg/kg was the median, so we lay right here. We didn't give these big, big doses of 20–50 mg/kg that these babies were getting in the Canadian NICUs. For me, in my head now, I keep the number of 2 mg/kg of morphine, and try to maintain below that level for any of our preterm infants to not impair cerebellar growth.

Encephalopathy of Prematurity



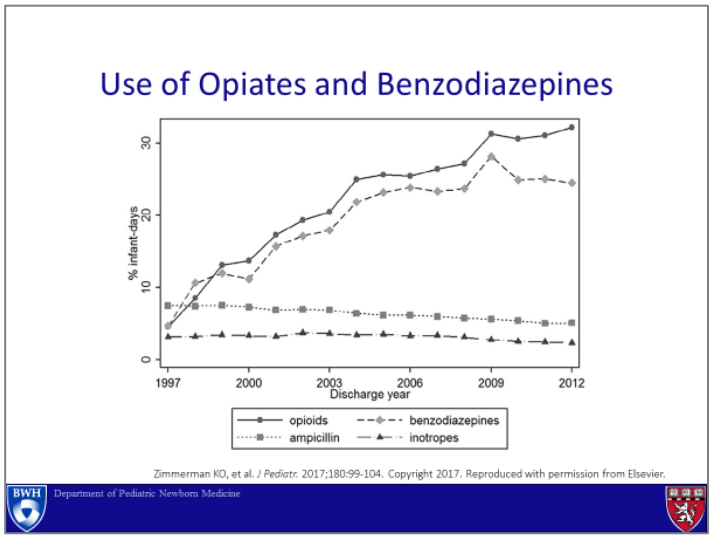
Slide 33

Fentanyl appears to be even worse. For those of you who thought, "Well, maybe I'll use something different," don't choose fentanyl! In St. Louis, we had 76% of our babies who received fentanyl, and again, this effect on the cerebellum, which is laden with opiate receptors and very sensitive. We also found an association with cerebellar hemorrhage.[11]



Slide 34

Why is this important? Because this is what is happening nationwide: We are using more and more of these medications, in terms of the exposure of our infants, because we are aware that some of our infants are distressed or stressed, and what we're doing is pulling for pharmacology.[12]



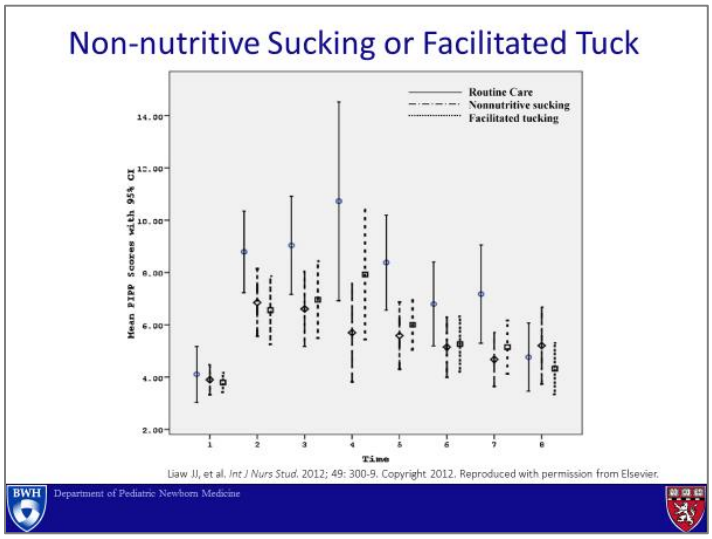
Slide 35

What I'd like to support is not drugs, but other methods of being able to reduce the experience of distress associated with the experience of the neonatal intensive care unit, such as facilitated tuck, music, kangaroo care, massage, or other types of support.

Slide 36

It's been shown here [Slide 37] in a very beautiful, simple study that just non-nutritive sucking and

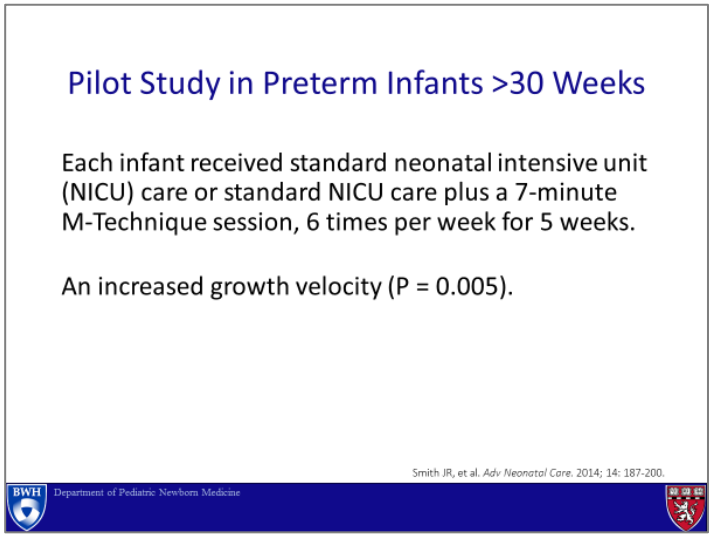
facilitated tucking can reduce pain scores for many minutes around a painful procedure.[13]



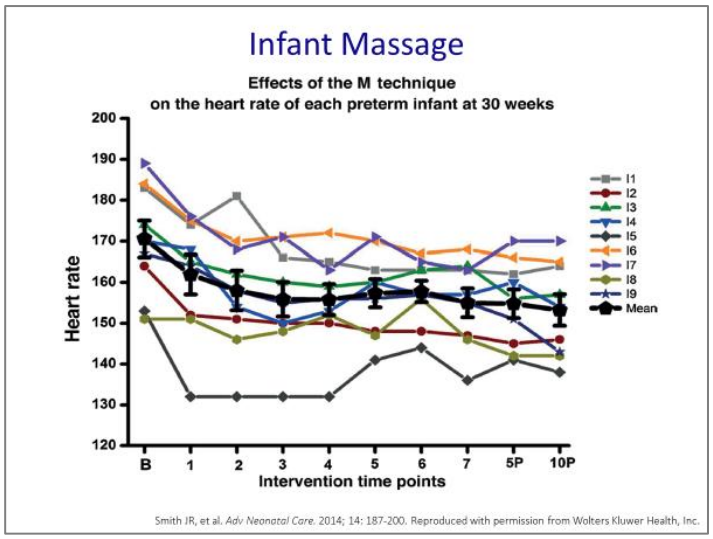
Slide 37

In fact, one of our nursing PhD students in St. Louis [Joan R. Smith] used a form of touch therapy, as well, and showed that even when an infant just received 7 minutes of this, 6 times/week, there was improvement in growth, and there were dramatic effects on the heart rate after the administration of the touch.[14]

Slide 38



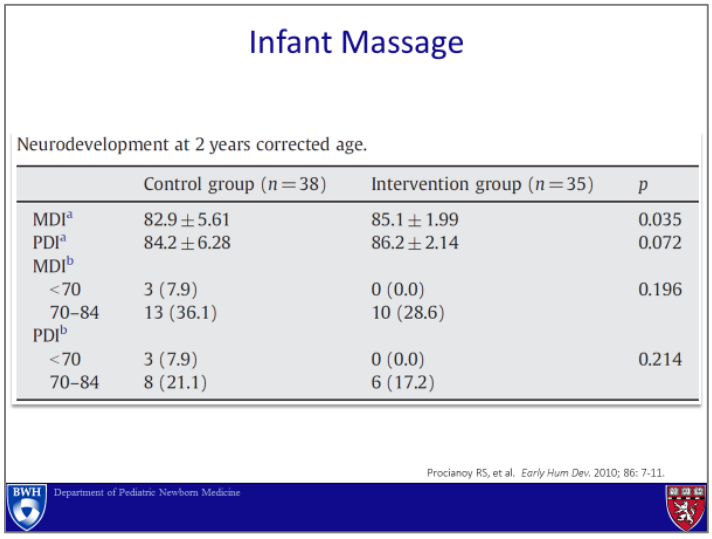
Slide 39



Slide 40

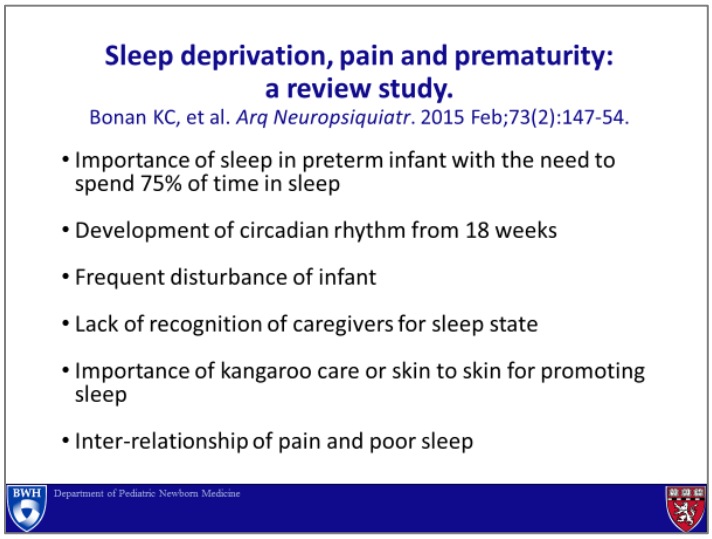
This has also been shown in others by infant massage with improved neurodevelopmental outcomes on follow-up 2 years after randomization to this treatment.[15]

Encephalopathy of Prematurity



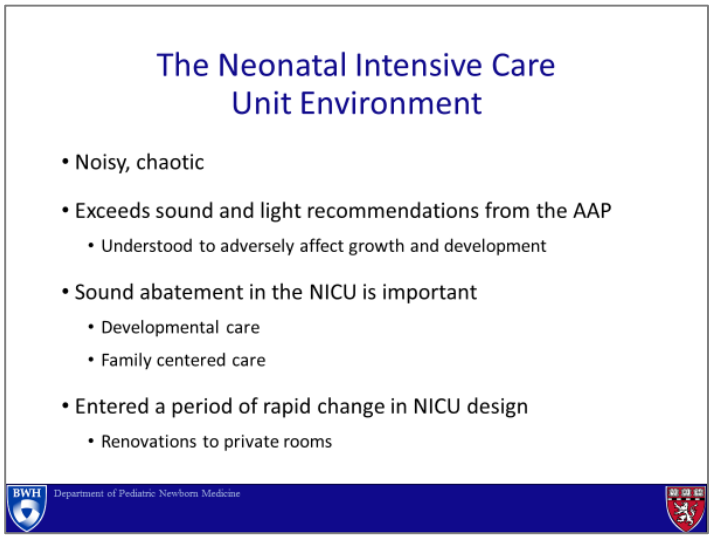
Slide 41

Sleep is something we are also starting to talk about in the NICU. We don't even monitor sleep, but it is probably critically important for typical brain development. The circadian rhythm is present from 18 weeks. People who have looked at this have shown that we interrupt our infants up to every 18 minutes in the first 2 weeks of their lives.[16] I'm not sure how good we'd feel tomorrow morning if we got interrupted every 18 minutes overnight tonight.



Slide 42

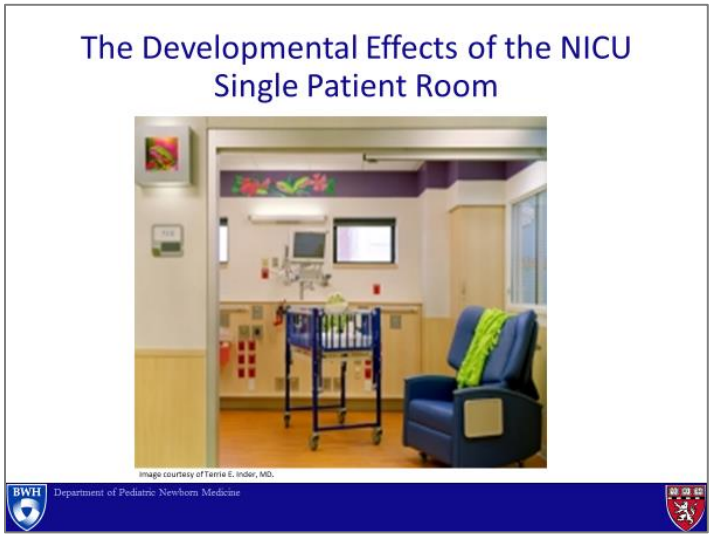
We had an experiment that we were able to undertake because we were interested in looking at the chaotic, noisy neonatal intensive care unit. We knew that we exceeded sound and light and other good environmental influences.



Slide 43

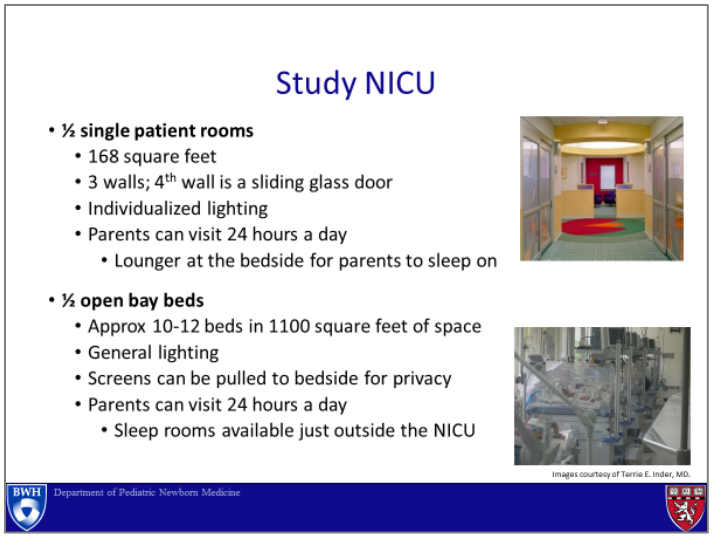
We were in the position where our NICU was being redesigned into a beautiful single-room environment. We undertook this study to show that putting babies into single rooms would decrease stress. I'll give you options tonight: you can go back to your nice little hotel room just on your own where you get to sleep quietly, or we have a dorm facility where we have 12 other people living in the same bedroom with you, and you can all hang out together. I think I know what you'd choose, right? The nice, single room. We thought the same thing for the baby.

Encephalopathy of Prematurity



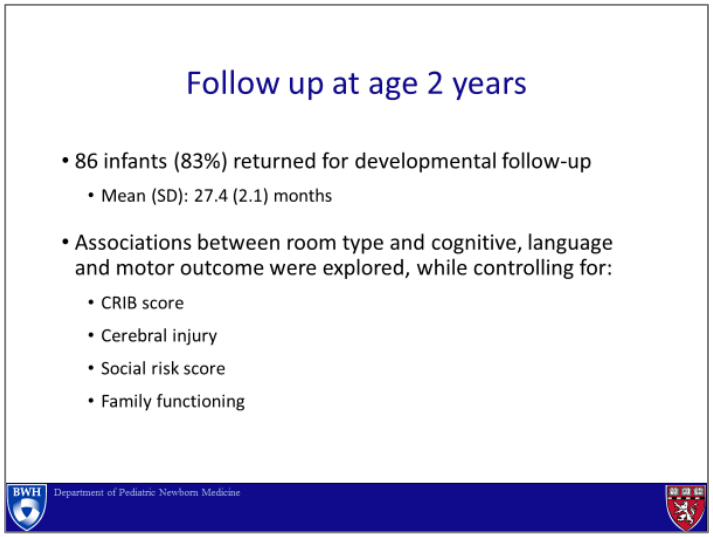
Slide 44

We had half of our unit that had been renovated to these beautiful single rooms and half that were still left open bay, and the parents could be present as much as they wanted.



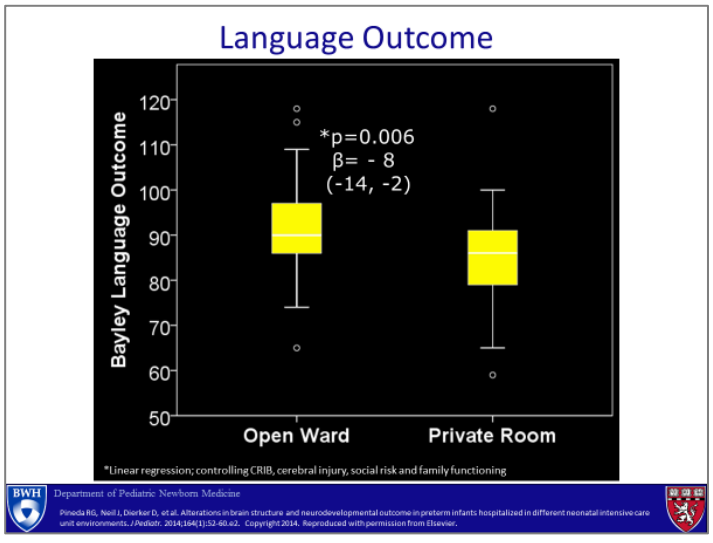
Slide 45

We followed our children up to show that being in a nice, single room would be so nice and so good for you. We looked at the association between room type and outcomes, controlling for various factors that were actually very similar between the groups.



Slide 46

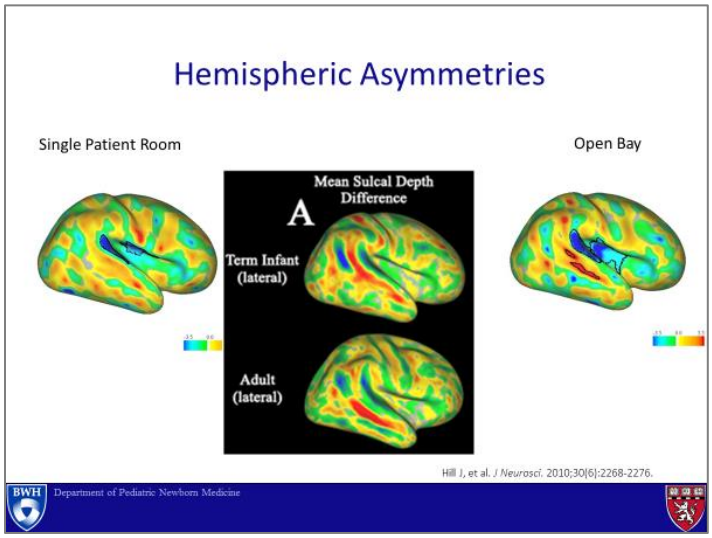
What did we find? This is why you do research, because it's not what you thought it was going to be, right? The private-room environment was associated with an 8 IQ point deficit in language outcome. We thought we were going to do better because they were going to be less stressed, and in fact, they did worse.[17]



Slide 47

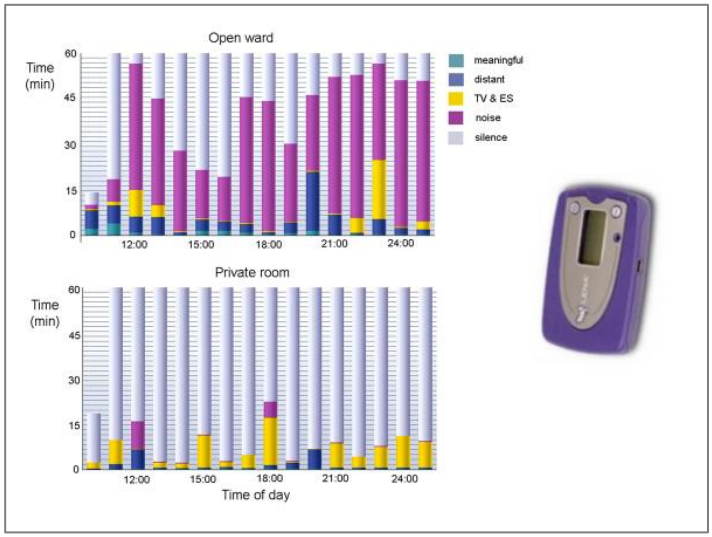
We looked at why they did worse, and we used our brain imaging to look at brain development. This is a pretty complicated slide [Slide 48]. If you look at the adult brain, what it shows is on the right in red,

you have a deeper temporal sulcus, and in the left in blue, you have a deeper temporal sulcus. The healthy term baby has exactly the same, even though they've never spoken a word and seen a face, it's exactly the same as the adult brain.[18] Whereas when you see the open bay, they're trying to form those differences between the hemispheres and in the single-family room, completely absent.



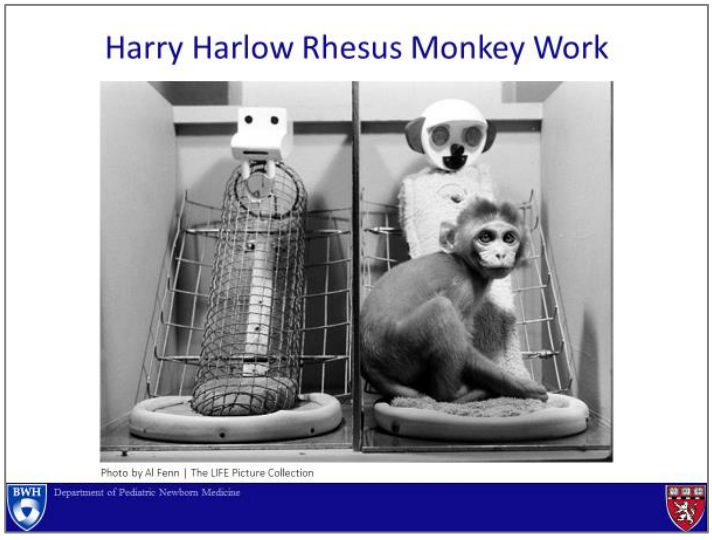
Slide 48

Our room environment in the NICU has structurally altered brain development. Why? Because look what you hear in the 2 different room environments [Slide 49]. In the open ward, you hear lots of noise, but the blue bars are language, human language. And, what you're hearing is nursing handover there where they're chatting like, "Oh, you've got to do this. You got to do that. Did you see that movie? It was great." In the private room, lots of silence. Lots and lots of silence.



Slide 49

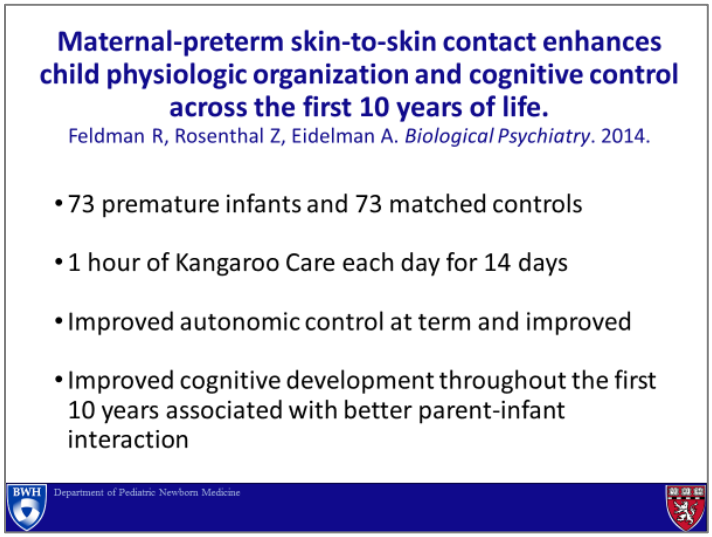
Alan Jobe wrote an editorial accompanying this,[19] and I want to emphasize, this is not just about auditory exposure. This takes us back to the 1950s when Harry Harlow wrote about the science of love and the importance of nurturing. [20]



Slide 50

We know even with skin-to-skin in a randomized trial, looking at just 1 hour of kangaroo care each day for 14 days, there was improved behavior at discharge, and improved development 10 years later.[21]

Encephalopathy of Prematurity



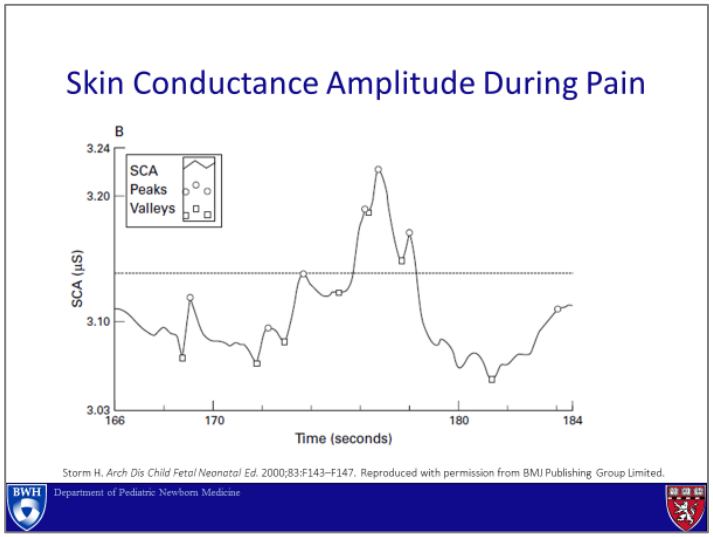
Slide 51

How can you measure stress or distress?

Well, a Norwegian company has developed a little device to measure skin conductance, which is actually a way of measuring lie detector technology.

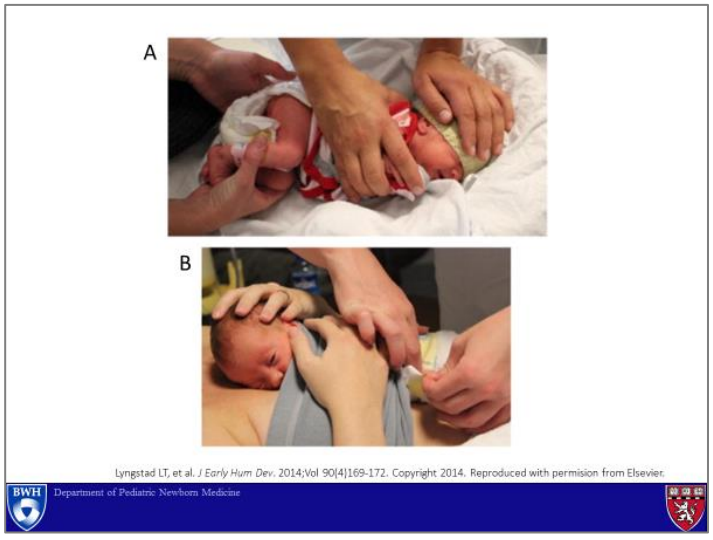
Slide 52

They measure the changes in skin resistance, and you can see here with a painful procedure, the peak going up. This is in a 22-week infant.[22]



Slide 53

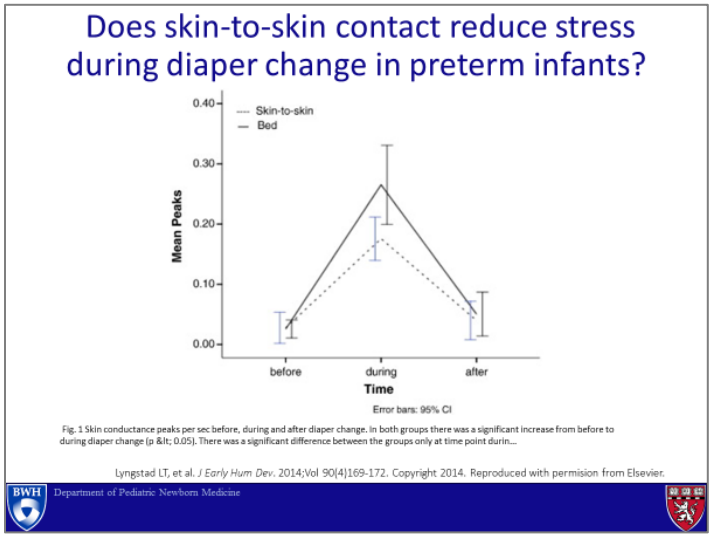
They also looked at it in things that we wouldn't regard as painful. Although, I would have to say, the *A* there [Slide 54] apparently is the way they change a diaper in Norway. I think it could be kind of painful the way that little guy's being held down.[23]



Slide 54

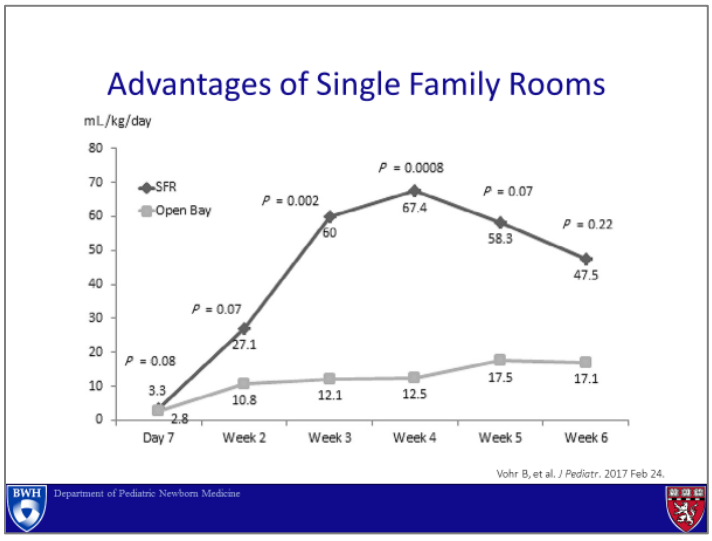
But they compared just a diaper change in the bed vs a diaper change on the mother's front, and showed differences in the level of distress the baby experienced, depending on whether the baby was held or changed in the bed.

Encephalopathy of Prematurity



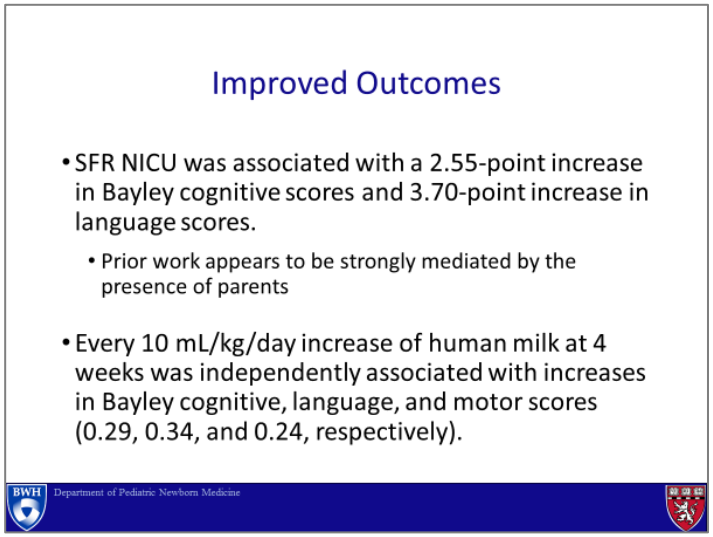
Slide 55

I don't want to leave you with the message that single-family rooms are all bad, because certainly my colleagues in Rhode Island have also studied and found improvement in developmental outcomes, mainly mediated by improved production of breast milk by the mothers and by improved parental presence.[24]



Slide 56

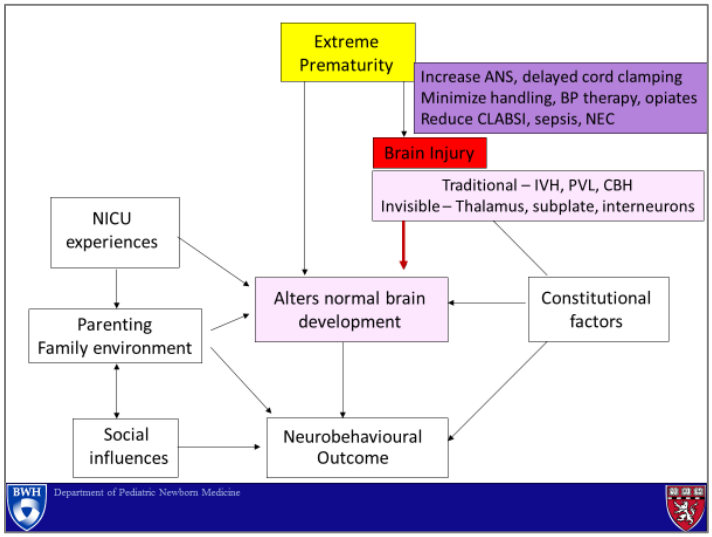
They've shown an increase in Bayley scores, but almost all mediated by the parent presence and by improved production of human milk.



Slide 57

In conclusion, I know we started with a little schema about the encephalopathy of prematurity and what was driving how to improve outcomes, and it started with brain injury. Remember, these traditional forms of brain injury are important, and I don't want to take away from that, but there's a lot of invisible brain injury, as well, that is altering brain development by these efferent and afferent effects. To be able to decrease that, we still need to work on increasing antenatal steroids (ANS), delayed cord clamping, minimizing handling, minimizing blood pressure therapy and opiates, reducing CLABSI and sepsis and NEC. All of these things will reduce the risk of brain injury.

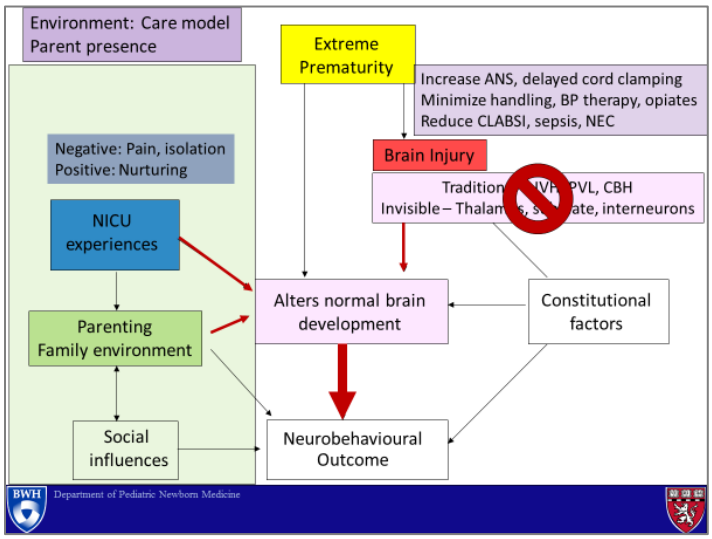
Encephalopathy of Prematurity



Slide 58

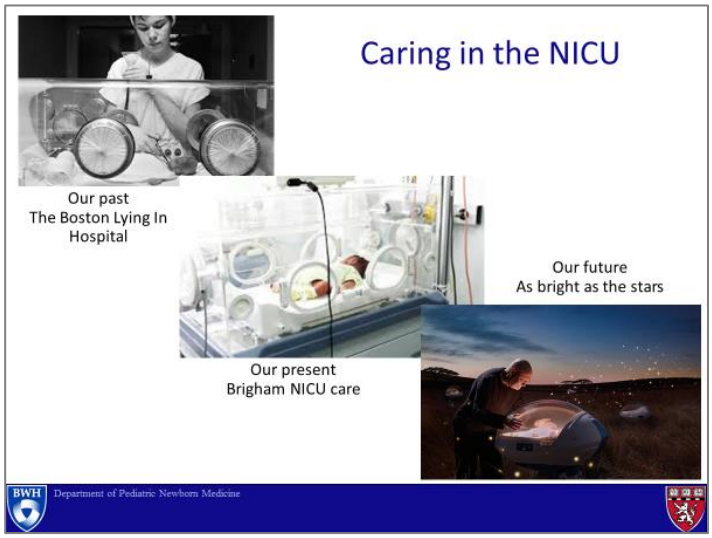
We also need to pay attention to NICU experiences, particularly the negative experiences of pain and isolation, and enhancing positive experiences of nurturing, because these also affect our parents who are dramatically affected by the NICU journey. These things are altering brain development just as much and influencing our outcomes.

Even if we took away all of the brain injury, if we don't address these by the environment—our care model and parent presence—we will not improve outcomes because we will continue to deviate away from typical brain development.



Slide 59

What should caring in the NICU look like? This [Slide 60, left] is the Boston Lying-In [Hospital], which our hospital was founded on. This our Brigham today [center]. I'm still not convinced that a plastic box is the right thing that we should be putting our babies into, even though it's great for short periods.



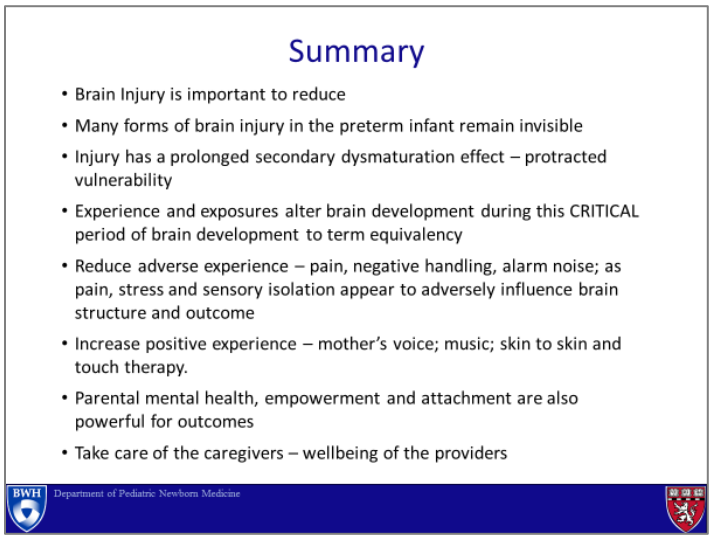
Slide 60

Maybe we need to be a bit more innovative as was shown most recently in a beautiful article by the *Wall Street Journal*.[25] This baby has no monitors on, but all of the readings are now on the outside of this very beautiful device. We need to partner and think outside the incubator box.

Slide 61

Encephalopathy of Prematurity

In summary, brain injury is important to reduce, and many forms of brain injury in the premature infant remain invisible. Injury has a prolonged secondary dysmaturation effect with protracted vulnerability. But I do want to leave [with] you that this period of brain development is critical, just as you heard about this period of lung development. You are forming the foundation for the rest of life. And, I hate to even propose, but we, as well as one other research group in the world now, are currently studying early degeneration in our preterm brains.



Slide 62

We need to reduce adverse experiences, such as pain, negative handling, alarm, as pain, stress, and sensory isolation influence adversely brain development. We need to increase positive experience: mother's voice, music, skin-to-skin, and touch.

Finally, parental mental health, empowerment, and attachment are powerful. And, we need to take care of the caregivers. The well-being of the providers is critically important, and most places around the world now are recognizing, we are one of the most burnout physician groups. We really aim to leave our families like this as they're discharged.

In closing, I just want to acknowledge that it's been a tremendous privilege to be part of this 42-year journey. The only thing that's unique about my presence this year is I'm not accompanied by one of my 3 favorite members of the family. My oldest daughter had the privilege of coming with me the first time I ever came from Australia to present here. We rented a convertible, went to Cape Canaveral, and now she has the privilege of launching rockets from Cape Canaveral with Space X. I think you had tremendous influence on my family. Thank you very much for your attention.

Slide 63

Encephalopathy of Prematurity

Abbreviations

CBH	cerebellar hemorrhage	**NICU**	neonatal intensive care unit
CLABSI	central line-associated bloodstream infection	**OL (pre-OL)**	premyelinating oligodendrocytes
CRIB	clinical risk index for babies	**PVL**	periventricular leukomalacia
GE	ganglionic eminence	**SFR**	single-family room
IVH	intraventricular hemorrhage	**SVZ**	subventricular zone
MDI	Mental Developmental Index	**VLBW**	very low birth weight
MRI	magnetic resonance imaging	**VPT**	very preterm
NEC	necrotizing enterocolitis		

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